

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 275 394 A2

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
15.01.2003 Bulletin 2003/03

(51) Int Cl.7: **A61K 31/565**

(21) Application number: **02254789.7**

(22) Date of filing: **09.07.2002**

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
IE IT LI LU MC NL PT SE SK TR**
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **10.07.2001 US 902389**

(71) Applicant: **MEDICAL COLLEGE OF HAMPTON
ROADS
Norfolk, VA 23507 (US)**

(72) Inventors:
• **Hodgen, Gary D.**
Virginia Beach, Virginia 23455 (US)
• **Anderson, Freedolph D.**
Virginia Beach, Virginia 23455 (US)
• **Williams, Robert F.**
Norfolk, Virginia 23503 (US)

(74) Representative: **Samuels, Lucy Alice
Gill Jennings & Every
Broadgate House
7 Eldon Street
London EC2M 7LH (GB)**

(54) **Ultra low dose oral contraceptives with sustained efficacy that induces amenorrhea**

(57) A method of female contraception involves administering a combination of estrogen and progestin continuously for more than a year in which the daily amounts of estrogen and progestin are equivalent to about 5-35 mcg of ethinyl estradiol and about 0.025 to 10 mg of norethindrone acetate, respectively. The advantages include lack of menstrual bleeding, less pa-

tient anemia, less total exposure to medication when compared to a 35 microgram (low dose) containing oral contraceptive, reduced risk of endometrial cancer, higher compliance rates and more lifestyle convenience for patients who desire less uterine bleeding each year or longer.

EP 1 275 394 A2

Description

BACKGROUND OF THE INVENTION

[0001] The ovarian/menstrual cycle is a complex event characterized by an estrogen rich follicular phase and, after ovulation, a progesterone rich luteal phase. Each has a duration of approximately 14 days resulting in an intermenstrual interval of about 28 days. The endometrial tissue responds to the changes in hormonal milieu.

[0002] The onset of menstruation is the beginning of a new menstrual cycle and is counted as day 1. During a span of about 5 to 7 days, the superficial layers of the endometrium, which grew and developed during the antecedent ovarian/menstrual cycle, are sloughed because demise of the extant corpus luteum in the non-fertile menstrual cycle is associated with a loss of progesterone secretion. Ovarian follicular maturation occurs progressively resulting in a rise in the circulating levels of estrogen, which in turn leads to new endometrial proliferation.

[0003] The dominant ovarian follicle undergoes ovulation near mid-cycle, generally between menstrual cycle days 12 to 16 and is converted from a predominantly estrogen source to a predominantly progesterone source (the corpus luteum). The increasing level of progesterone in the blood converts the proliferative endometrium to a secretory phase in which the tissue proliferation has promptly abated, leading to the formation of endometrial glands or organs. When the ovulated oocyte is viably fertilized and continues its progressive embryonic cleavage, the secretory endometrium and the conceptus can interact to bring about implantation (nidation), beginning about 6 to 8 days after fertilization.

[0004] If an ongoing pregnancy is to be established via implantation, the embryo will attach and burrow into the secretory endometrium and begin to produce human chorionic gonadotropin (HCG). The HCG in turn stimulates extended corpus luteum function, i.e. the progesterone production remains elevated, and, in turn, menses does not occur in the fertile menstrual cycle. Pregnancy, typically, can then be established.

[0005] In the non-fertile menstrual cycle, the waning level of progesterone in the blood causes the endometrial tissue to be sloughed. This starts a subsequent menstrual cycle.

[0006] Because endometrial proliferation serves to prepare the uterus for an impending pregnancy, manipulation of hormones and of the uterine environment can provide contraception. For example, estrogens are known to decrease follicle stimulating hormone secretion by feedback inhibition. Under certain circumstances, estrogens can also inhibit luteinizing hormone secretion, once again by negative feedback. Under normal circumstances, the spike of circulating estrogen found just prior to ovulation induces the surge of gonadotropic hormones that occurs just prior to and resulting in ovu-

lation. High doses of estrogen immediately post-coitally also can prevent conception probably due to interference with implantation.

[0007] Progestins can also provide contraception. Endogenous progesterone after estrogen is responsible for the progestational changes of the endometrium and the cyclic changes of cells and tissue in the cervix and the vagina. Administration of progestin makes the cervical mucus thick, tenacious and cellular which is believed to impede spermatozoal transport. Administration of progestin also inhibits luteinizing hormone secretion and blocks ovulation in humans.

[0008] The most prevalent form of oral contraception is a pill that combines both an estrogen and a progestin, a so-called combined oral contraceptive preparation.

[0009] Alternatively, there are contraceptive preparations that comprise progestin only. However, the progestin-only preparations have a more varied spectrum of side effects than do the combined preparations, especially more breakthrough bleeding. As a result, the combined preparations are the preferred oral contraceptives in use today (Sheth et al., *Contraception* 25:243, 1982).

[0010] Whereas the conventional 21 day pill packs with a 7 day "pill free" or placebo interval worked well when oral contraceptives were of higher dosage, as the doses have come down, for both the estrogen and progestin components, bleeding problems have increased in frequency, especially in the early months of oral contraceptive use, but even persistently so in some patients. Since the advent of combined estrogen-progestin medications as oral contraceptives, there has been a steady downward adjustment of the daily estrogen dosage. Concurrently, where exposure to the progestin component has also been lowered, reduced androgenicity has remained an ongoing priority. Together these adaptations in formulation have been presented in a variety of regimens, both monophasic and multiphasic. Each have their own advantages and disadvantages. All-in-all, today's oral contraceptives are much safer with regard to the incidence and severity of estrogen-linked clotting disorders as well as the suggested cumulative impact of more "lipid friendly" progestins that maintain the potentially advantageous high density lipoprotein cholesterol levels in circulation.

[0011] U.S. Patent 4,390,531 teaches a triphasic regimen in which each phase uses about 20-40 mcg ethinyl estradiol, phases 1 and 3 use 0.3-0.8 norethindrone and phase 2 doubles the amount of the norethindrone. These three phases consume 21 days of a 28 day treatment cycle. European published application 0 226 279 states that this regimen is associated with a high incidence of breakthrough bleeding and substitutes a three phase oral contraceptive regimen using a relatively low amount of ethinyl estradiol (10-50 µg) and a relatively high amount of norethindrone acetate (0.5-1.5 mg) in each phase provided that the amount of estrogen in any two phases is never the same. A "rest" phase of about 7 days is used in this regimen.

[0012] U.S. Patent 5,098,714 teaches an osmotic, oral dosage form. One "pill" is administered per day but the administration is, in effect, polyphasic. The dosage form is constructed such that it provides an initial pulse delivery of estrogen and progestin followed by prolonged delivery of estrogen.

[0013] European published patent application 0 253 607 describes a monophasic contraceptive preparation containing units having 0.008-0.03 mg of ethinyl estradiol and 0.025-0.1 mg of desogestrel (or equivalent) and a regimen where the preparation is administered over a 23-25 day period, preferably 24 days, followed by a 2-5 day pill-free period. The object of this regimen is to provide hormonal replacement therapy and contraceptive protection for the pre-menopausal woman in need thereof by supplying a low dose of an estrogen combined with a "very low dose of a progestogen."

[0014] In 1989, the accumulating data from the evolution of oral contraceptive pill formulations containing only 20-35 µg of estrogen per day spurred the Food and Drug Administration's Fertility and Maternal Health Drugs Advisory Committee to recommend indication of low dose oral contraceptives for healthy, non-smoking women even during the perimenopausal years, such as, for instance, ages 35-50. In Japan, oral contraceptives have recently been approved for the first time.

[0015] U.S. patent number 5,552,394 describes a method of female contraception which is characterized by a reduced incidence of breakthrough bleeding after the first cycle involves monophasically administering a combination of estrogen and progestin for 23-25 consecutive days of a 28 day cycle in which the daily amounts of estrogen and progestin are equivalent to about 5-35 mcg of ethinyl estradiol and about 0.025 to 10 mg of norethindrone acetate, respectively and in which the weight ratio of estrogen to progestin is at least 1:45 calculated as ethinyl estradiol to norethindrone acetate.

[0016] In establishing a estrogen-progestin regimen for oral contraceptives, two principal issues must be confronted. First, efficacy must be maintained and second, there must be avoidance of further erosion in the control of endometrial bleeding. In general, even the lowest dose oral contraceptive products commercially available have demonstrated efficacy but the overall instances of bleeding control problems has increased as the doses were reduced, as manifest both in breakthrough bleeding (untimely flow or spotting) or withdrawal amenorrhea during the "pill free" week (expected menses).

[0017] It is the object of the present invention to provide a new estrogen-progestin combination and/or regimen for oral contraceptive use which maintains the efficacy and provides enhanced control of endometrial bleeding, the continuous use of which leads to amenorrhea (a lack of vaginal bleeding). The regimen enhances compliance by eliminating stop/start and also reduces or eliminates vaginal blood loss in patients, thereby re-

ducing or eliminating the chances of anemia. Eliminating menstrual intervals can enhance lifestyles and convenience. This and other objects of the invention will become apparent to those skilled in the art from the following detailed description.

[0018] U.S. patent number 5,898,032 describes a method of female contraception which involves administering, preferably monophasically, a combination of estrogen and progestin for 60-110 consecutive days followed by 3-10 days of no administration, in which the daily amounts of the estrogen and progestin are equivalent to about 5-35 mcg of ethinyl estradiol and about 0.025-10 mg of norethindrone acetate, respectively. It has now been found that the continuous administration of the combination can be extended to greater than one year. The duration determined by the patients medical condition and/or needs with efficacy being maintained and the induction of amenorrhea (lack of bleeding) avoids the medical problem of anemia. Moreover, symptoms which are generally attributed to hormone withdrawal (such as headaches, irritability, sleeplessness, cramps, and pelvic pressure, among others) can be avoided. Relative to women having natural or oral contraceptive-induced menstruation, the incidence of endometrial cancer will be reduced. Administration of agents to control endometriosis for this long period of time is known but this is the first time an oral contraceptive protocol of this length has been found.

SUMMARY OF THE INVENTION

[0019] This invention relates to a method of female contraception which is characterized by eliminating withdrawal menses. More particularly, it relates to a method of female contraception which involves administering, preferably monophasically, a combination of estrogen and progestin continuously for more than a year in which the daily amounts of the estrogen and progestin are equivalent to about 5-35 mcg of ethinyl estradiol and about 0.025-10 mg of norethindrone acetate, respectively.

DESCRIPTION OF INVENTION

[0020] In accordance with the present invention, a woman in need of contraception is administered a combined dosage form of estrogen and progestin, preferably monophasically, continuously for more than a year in which the daily amounts of estrogen and progestin are equivalent to about 5-35 mcg of ethinyl estradiol and about 0.025 to 10 mg of norethindrone acetate, respectively. The time duration is preferably at least about 1, 1 years, more preferably at least about 1.25 or about 1.5 years, and can continue for about 5 years or more.

[0021] The preferred progestin and estrogen are norethindrone acetate and ethinyl estradiol, although other estrogens and progestins can be employed. The weight ratio of these two active ingredients is between

10 and 50, depending on the potency of the progestin. For example, levonorgestrel is believed to be approximately 10 times more potent than norethindrone or its acetate, so the weight in micrograms administered would be multiplied by 10 to calculate the progestin to estrogen ratio. The preferable amount of ethinyl estradiol is about 10-30 mcg and the preferable amount of the norethindrone acetate is about 0.25-1.5 mg. Other estrogens vary in potency from ethinyl estradiol. For example, 30 mcg of ethinyl estradiol is roughly equivalent to 60 mcg of mestranol or 2,000 mg of 17 β -estradiol. Likewise, other progestins vary in potency from norethindrone acetate. Thus, 3.5 mg of norethindrone acetate is roughly equivalent to 1 mg of levonorgestrel or desogestrel and 3-ketodesogestrel and about 0.7 mg of gestodene. The values given above are for the ethinyl estradiol and the norethindrone acetate and if a different estrogen or progestin is employed, an adjustment in the amount based on the relative potency should be made. The correlations in potency between the various estrogens and progestins are known.

[0022] Other useable estrogens include the esters of estradiol, estrone and ethinyl estradiol such as the acetate, sulfate, valerate or benzoate, conjugated equine estrogens, agnostic anti-estrogens, and selective estrogen receptor modulators. The estrogen is administered in the conventional manner by any route where it is active, for instance orally or transdermally. Most estrogens are orally active and that route of administration is therefore preferred. Accordingly, administration forms can be tablets, dragees, capsules or pills which contain the estrogen (and preferably the progestin) and a suitable pharmaceutically acceptable carrier.

[0023] Pharmaceutical formulations containing the progestin and a suitable carrier can be solid dosage forms which includes tablets, capsules, cachets, pellets, pills, powders or granules; topical dosage forms which includes solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels or jellies, foams and controlled release depot entities; and parenteral dosage forms which includes solutions, suspensions, emulsions or dry powder comprising an effective amount of progestin as taught in this invention. It is known in the art that the active ingredient, the progestin, can be contained in such formulations in addition to pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, "Modern Pharmaceutics", Banker & Rhodes, Marcel Dekker, Inc. 1979; "Goodman & Gilman's The Pharmaceutical Basis of Therapeutics", 6th Edition, MacMillan Publishing Co., New York 1980 can be consulted.

[0024] The pharmaceutical formulations may be provided in kit form containing sufficient tablets intended for

ingestion on successive days continuously to be obtained in amounts sufficient to insure continuous use until another supply can be obtained or the patient desires to discontinue the method. For example, medication could be supplied in packets of 30, 60 or 90, etc. depending on the patients desires as to how much medication she wants available.

[0025] In order to further illustrate the present invention, specific examples are set forth below. It will be appreciated, however, that these examples are illustrative only and are not intended to limit the scope of the invention.

EXAMPLE 1

[0026] A study is carried out at a fully accredited animal research facility which complies through its animal care and use committee with the review standards set forth in the National Institute of Health's "Guide for Care and Use of Laboratory Animals", the Public Health Services' "Principles for the Care and Use of Laboratory Animals", and the United States Department of Agriculture's Implementation Regulations of the 1985 Amendments for the Animal Welfare Act.

[0027] Ten adult female cynomolgus monkeys (*Macaca fascicularis*) having regular presumably ovulatory menstrual cycles (28.9 ± 3.1 days for the month prior to study entry) are selected. Their duration of spontaneous menses is 3.4 ± 1.4 days. Mean body weight of the monkeys is 3.5 ± 1.1 kg ($X \pm SEM$). They are housed individually in a controlled environment (12 hours of light and 23 °C). Their diet is a commercial primate food (Purina, St. Louis, MO) with water *ad libitum*.

[0028] The monkeys are divided at random into two groups (N=5 each). The studies begin with spontaneous menstruation in a pretreatment control cycle. At the onset of the next spontaneous menses, alternatively, they are assigned to receive on cycle day one an ultra low dose oral contraceptive continuously for more than one year. The study concludes with each group of primates being followed during a post-treatment spontaneous ovarian menstrual cycle.

[0029] Femoral blood is collected weekly and the serum frozen for subsequent RIA of estradiol, progesterone, FSH and LH in the pretreatment, treatment, and post-treatment phase. s Bleeding profiles are kept by daily vaginal swabs, indicating spontaneous menstruation, withdrawal bleeding, breakthrough bleeding, or amenorrhea. Breakthrough bleeding is defined as detectable blood in the vagina outside of the first 8 days after the last dose of oral contraceptive or the onset of spontaneous menses in non-treatment cycles.

[0030] Since the objective is to test an ultra low dose oral contraceptive, the medication is adjusted to fit the smaller (than human) body weight of these laboratory primates. The dose of ethinyl estradiol is 1.2 μ g/day, while the dose of norethindrone acetate is 0.06 mg/day. This "in-house" reformulation is achieved by grinding to

powder a commercially available monophasic pill (Loestrin 1/20, Parke Davis, Morris Plains, NJ), which originally contained 1 mg of norethindrone acetate and 20 µg of ethinyl estradiol per tablet, contained in a conventional 21 day pack along with 7 iron-containing placebo tablets.

EXAMPLES 2 - 5

[0031] The example 1 procedure is repeated using the following combinations of estrogen and progestin:

Example	Estrogen	Progestin
2	mestranol	levo-norgestrel
3	17-beta-estradiol	3-keto-desogestrel
4	ethinyl estradiol	desogestrel
5	mestranol	gestodone

[0032] Application of the compounds, compositions and methods of the present invention for the medical or pharmaceutical uses described can be accomplished by any clinical, medical, and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. It will therefore be appreciated that the various embodiments which have been described above are intended to illustrate the invention and various changes and modifications can be made in the inventive method without departing from the spirit and scope thereof.

Claims

1. A method of female contraception which comprises monophasically administering a combination of estrogen and progestin continuously for more than a year, in which the daily amounts of estrogen and progestin are equivalent to about 5-35 mcg of ethinyl estradiol and about 0.025 to 10 mg of norethindrone acetate, respectively,
2. The method of claim 1 in which the daily amount of estrogen is equivalent to about 10 to 30 mcg of ethinyl estradiol.
3. The method of claim 2 in which the daily amount of progestin is equivalent to 0.25-1.5 mg of norethindrone acetate.
4. The method of claim 3 in which the combination is administered for at least 370 consecutive days.
5. The method of claim 4 in which the estrogen is ethinyl estradiol.
6. The method of claim 5 in which the progestin is norethindrone acetate.
7. The method of claim 1 in which the daily amount of progestin is equivalent to 0.25-1.5 mg of norethindrone acetate.
8. The method of claim 1 in which the combination is administered for at least 370 consecutive days.
9. The method of claim 1 in which the estrogen is ethinyl estradiol.
10. The method of claim 1 in which the progestin is norethindrone acetate.
11. The method of claim 1 in which the daily amount of estrogen is up to 30 mcg of ethinyl estradiol.

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 275 394 A3

(12)

EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
29.01.2003 Bulletin 2003/05

(51) Int Cl.7: **A61K 31/565, A61K 31/569**

(43) Date of publication A2:
15.01.2003 Bulletin 2003/03

(21) Application number: **02254789.7**

(22) Date of filing: **09.07.2002**

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
IE IT LI LU MC NL PT SE SK TR**
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **10.07.2001 US 902389**

(71) Applicant: **MEDICAL COLLEGE OF HAMPTON
ROADS
Norfolk, VA 23507 (US)**

(72) Inventors:
• **Hodgen, Gary D.**
Virginia Beach, Virginia 23455 (US)
• **Anderson, Freedolph D.**
Virginia Beach, Virginia 23455 (US)
• **Williams, Robert F.**
Norfolk, Virginia 23503 (US)

(74) Representative: **Samuels, Lucy Alice**
Gill Jennings & Every
Broadgate House
7 Eldon Street
London EC2M 7LH (GB)

(54) **Ultra low dose oral contraceptives with sustained efficacy that induces amenorrhea**

(57) A method of female contraception involves administering a combination of estrogen and progestin continuously for more than a year in which the daily amounts of estrogen and progestin are equivalent to about 5-35 mcg of ethinyl estradiol and about 0.025 to 10 mg of norethindrone acetate, respectively. The advantages include lack of menstrual bleeding, less pa-

tient anemia, less total exposure to medication when compared to a 35 microgram (low dose) containing oral contraceptive, reduced risk of endometrial cancer, higher compliance rates and more lifestyle convenience for patients who desire less uterine bleeding each year or longer.

EP 1 275 394 A3



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 02 25 4789

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X,D	EP 0 911 029 A (HAMPTON ROADS MEDICAL COLLEGE) 28 April 1999 (1999-04-28)	1-3,7, 9-11	A61K31/565 A61K31/569
Y	* the whole document *	4-6,8	
X	US 5 208 225 A (BOISSONNEAULT ROGER M ET AL) 4 May 1993 (1993-05-04) * page 3, column 3, line 51 - page 3, column 4, line 2; claims 1-6; table II * * column 4, line 4 * * column 4, line 20 * * column 11, line 9 - line 15 * * column 11, line 44 - line 47 *	1-3,7, 9-11	
Y	---	4-6,8	
X	RUBIO-LOTVIN B ET AL: "Desogestrel-ethynylestradiol, an oral monophasic contraceptive clinical and lipid metabolic effects: A 5-year experience." 1992, ADVANCES IN CONTRACEPTIVE DELIVERY SYSTEMS, VOL. 8, NR. 1-2, PAGE(S) 75-88 XP009000504 ISSN: 1012-8689 * abstract * * page 76, paragraphs 4,7 * ---	1-11	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61K
-/--			
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 9 December 2002	Examiner Ansaldo, M
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document</p> <p>T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons &: member of the same patent family, corresponding document</p>			

EPO FORM 1503 (01.02) (P04C01)



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 02 25 4789

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Y	<p>SULAK P ET AL: "CLINICAL COMPARISON OF TRIPHASIC NORGESTIMATE /35 MUG ETHINYL ESTRADIOL AND MONOPHASIC NORETHINDRONE ACETATE/20 MUG ETHINYL ESTRADIOL", CONTRACEPTION, GERON-X, INC., LOS ALTOS, CA, US, VOL. 59, NR. 3, PAGE(S) 161-166 XP000881615 ISSN: 0010-7824 * abstract * * page 161, column 2, line 13, paragraph 2 * * page 162, column 2, paragraph 2 * * page 166, column 1, paragraph 5 * * page 166, column 2, paragraph 2 *</p>	1-11	
Y	<p>US 5 552 394 A (HODGEN GARY D) 3 September 1996 (1996-09-03) * abstract * * column 3, paragraph 3 * * column 3, line 45 - line 47 * * claims 1,2,5-7,10-12 *</p>	1-11	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 9 December 2002	Examiner Ansaldo, M
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03.82 (P04C01)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 02 25 4789

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

09-12-2002

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0911029	A	28-04-1999	US 5898032 A	27-04-1999
			AT 216241 T	15-05-2002
			DE 69804918 D1	23-05-2002
			DE 69804918 T2	07-11-2002
			DK 911029 T3	17-06-2002
			EP 0911029 A2	28-04-1999
			JP 11029481 A	02-02-1999
			NO 982815 A	28-12-1998
US 5208225	A	04-05-1993	AT 94392 T	15-10-1993
			AU 599082 B2	12-07-1990
			AU 6913087 A	03-09-1987
			CA 1300017 A1	05-05-1992
			DE 3787386 D1	21-10-1993
			DE 3787386 T2	05-05-1994
			DK 99987 A	28-08-1987
			EP 0235090 A1	02-09-1987
			ES 2059403 T3	16-11-1994
			HK 182795 A	08-12-1995
			JP 2942560 B2	30-08-1999
			JP 62205024 A	09-09-1987
			ZA 8700332 A	26-08-1987
US 5552394	A	03-09-1996	NONE	